Drug Design, Development and Therapy

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REVIEW

Mechanism involved in insulin resistance via accumulation of β-amyloid and neurofibrillary tangles: link between type 2 diabetes and Alzheimer's disease

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Abstract: The pathophysiological link between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) has been suggested in several reports. Few findings suggest that T2DM has strong link in the development process of AD, and the complete mechanism is yet to be revealed. Formation of amyloid plaques (APs) and neurofibrillary tangles (NFTs) are two central hallmarks in the AD. APs are the dense composites of β-amyloid protein (Aβ) which accumulates around the nerve cells. Moreover, NFTs are the twisted fibers containing hyperphosphorylated tau proteins present in certain residues of Aβ that build up inside the brain cells. Certain factors contribute to the aetiogenesis of AD by regulating insulin signaling pathway in the brain and accelerating the formation of neurotoxic Aβ and NFTs via various mechanisms, including GSK3β, JNK, CamKII, CDK5, CK1, MARK4, PLK2, Syk, DYRK1A, PPP, and P70S6K. Progression to AD could be influenced by insulin signaling pathway that is affected due to T2DM. Interestingly, NFTs and APs lead to the impairment of several crucial cascades, such as synaptogenesis, neurotrophy, and apoptosis, which are regulated by insulin, cholesterol, and glucose metabolism. The investigation of the molecular cascades through insulin functions in brain contributes to probe and perceive progressions of diabetes to AD. This review elaborates the molecular insights that would help to further understand the potential mechanisms linking T2DM and AD.

Keywords: Alzheimer's disease, type 2 diabetes mellitus, insulin deficiency, insulin signaling pathway, cholesterol

Introduction

Many reports suggest a strong pathophysiological links between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD). Prevalence of T2DM and its associated complications leads to AD that increases with time in the aging population, with profound oxidative stress (OS) potentially relating the molecular mechanisms involved in T2DM–AD linkage.[1,2] Insulin action in the brain stimulates the modulation of numerous molecular cascades, such as cholesterol metabolism, energy expenditure, glucose homeostasis, feeding behavior, synaptogenesis, neurotrophy, neurotransmitters, cognition, memory, inflammation, apoptosis, and reproduction.[3] In addition, insulin regulates the metabolism of peripheral β-amyloid peptide (Aβ) and hyperphosphorylated tau protein. In AD, the extracellular accumulation of Aβ plaques, intracellular aggregation of hyperphosphorylated tau protein in neurofibrillary tangles (NFTs), and neuronal loss occur in the cortex and hippocampus.[4,5] Hence, the disruption of insulin

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functions in diabetic conditions, like hyperinsulinemia and hyperglycemia, interrupts insulin signaling involved in the clearance of Aβ plaques and NFTs pathology. This leads to the accelerated formation of neurotoxic Aβ and NFTs via various mechanisms, including GSK3β, JNK, CamKII, CDK5, CK1, MARK4, PLK2, Syk, DYRK1A, PPP, and P70S6K contributing to the aetiogenesis of AD.[1,2,6] In this review, we discuss the roles of aberrant brain insulin signaling in T2DM leading to AD and the mechanisms in the deposition of Aβ and NFTs and their therapeutic potential in restoring the brain pathways that might contribute to T2DM and AD treatment.

Insulin hormone linking type 2 diabetes and AD

The excessive insulin finds way into the brain and interrupts the biochemistry.[7–9] One of the possible mechanisms could be the modification of insulin signaling involved in a variety of neuronal functions of brain, such as abnormal protein O-GlcNAcylation, alteration of mitochondria, OS, glucose metabolism, and cholesterol, as well as amyloid plaques (APs) formation, changed Aβ metabolism, and tau hyperphosphorylation protein deposition.[1,8,10] Reduced insulin plasma levels in T2DM can impair this signaling pathway forming two core neuropathological hallmarks of AD, ie, NFTs and Aβ plaque, which leads to impaired memory and cognitive dysfunction.[11,12] The progression of diabetes to AD and their molecular cascades involved in the function of insulin are discussed below (Table 1).

Insulin and brain

Regulation of carbohydrate and fat metabolism is mediated by insulin hormone via stimulating the absorption of glucose from the blood to fat tissue and skeletal muscles. Disturbance in insulin in the periphery system may cause diabetic mellitus (DM), but in the brain develop certain neurodegenerative states like mild cognitive impairment (MCI) and AD. However, brain itself can also synthesize some portion of insulin and crosses the blood–brain barrier (BBB) through a saturable transporter within the central nervous system (CNS) that affects feeding and cognition through CNS mechanisms that are independent of glucose utilization.[3,8,13,14] Studies on the mechanisms of insulin production and secretion in the CNS show similarities between beta cells and neurons, remarkably in the context of ATP-sensitive K+ (KATP) channel depolarization.[15,16] Increased number of insulin receptors (IRs) during cell differentiation in the brain recommends important role of IR signaling in neuronal proliferation during development, maturation, regeneration of axons, and neurite outgrowth in developing neurons projections as they grow (Figure 1).[8,17,18]

Cholesterol metabolism

Cholesterol which is metabolized in the brain plays a crucial role in cell membrane, independent from peripheral tissues featuring BBB, where it plays important membrane function, acts as an antioxidant, and serves as the raw material to produce steroidal progesterone which modulates neuroendocrine functions that alter physiology and behavior in the CNS. Interestingly, in adipose tissue breakdown of fat is inhibited by insulin which is responsible for the intracellular lipase inhibition that demands triglycerides to hydrolyze and release fatty acids. Moreover, insulin stimulates entry of glucose into adipocytes to synthesize glycerol within the cells, thereby enhancing the rate of glucose translocation across the cell membrane, muscles, and in adipose tissue. Then, apolipoprotein E (ApoE)-cholesterol particle is processed to free the cholesterol in the lysosomes and is then transported to the membrane. ApoE isoform ε4 is the most common risk factor for AD that correlates with escalation of Aβ clearance and accumulation in the brain during AD.[19–22] Thus, insulin alteration in diabetes can interrupt brain cholesterol metabolism leading to metabolic dysfunction, thereby causing neurological disorders (Figure 2).[23]

Glucose uptake

Uptake of glucose, the main fuel in body, varies among the tissues depending on the tissue metabolic needs and glucose availability. The glucose transporter (GLUT) protein isoforms are involved in facilitating the translocation of glucose in which the prominent isoforms are GLUT1-4. Glucose uptake is stimulated by the movement of GLUT4 transporters from the intracellular membrane into the plasma membrane which demands GLUT4-containing vesicles to facilitate the process.[24] In the kidney, glucose uptake is accomplished by the secondary active transport mechanism through GLUT2 transporter, linked to Na+/K+ pump reliant on the sodium gradient generated by NaKATPase. Malfunctioning of GLUT4 protein in the hippocampus affects the biochemical reactions and cognitive flexibility offered by hippocampal neurons, thus developing depression and lowering the cognitive function which in turn increases the risk of Alzheimer development (Figure 3).[25–27]

GLUT function can be regulated by insulin-like growth factor (IGF) family. IGF is very close to the natural human growth hormone and consists of three ligands (insulin, IGF-1, and IGF-2), six IRs (IRα [fetal], IRβ [adult], IGF-1 receptor [IGF-1R], IGF-2R, hybrid IGF-1R/IRα, hybrid IGF-1R/IRβ),

Table 1 Effect of insulin on brain: decrease of insulin via various pathways could lead to the effects on the brain which in turn contributes to Alzheimer's disease

Region	Effect of insulin	Progress of insulin action	Ref
Peripheral tissues, hippocampus	Regulation of glucose homeostasis through relationship between brain insulin receptors and neurotransmitters	1. Induced neuronal norepinephrine inhibition and serotonin reuptake stimulation 2. Increased food intake in the insulin resistance to facilitate peripheral elevation of free fatty acids and release of proinflammatory cytokines 3. Reduced O-GlcNAcylation of tau in brain hypometabolism and increased tau phosphorylation and NFTs formation in AD 4. Impaired mitochondrial function and thiamine-dependent processes in the cerebral glucose hypometabolism of AD 5. Diminished insulin efficiency to block the glucose formation 6. Induced opening of ATP-sensitive K^+ channels leading to cell hyperpolarization	8, 191–193
Hypothalamus	Production of liver glucose stimulus of the acute nucleus	1. Stimulus transmission to the vagal motor nucleus nerve to produce appropriate response in the liver 2. Decreased insulin inhibitory effect on the glucose hepatic production	194–198
Neurons and glial cells	Induction of forebrain neuron growth and differentiation and NGF to stimulate neuritis formation	Associated to the cerebral insulin actions, including cell growth	
Hippocampus (CA1)	Induction of PSD-95 expression, a dendritic scaffolding protein	Activated PI3K/mTOR pathway	199
Hippocampus (CA1)	Synaptogenesis, synaptic function modulation, and regulation of dendritic spine formation and excitatory synapse development	1. Upregulated Tau protein 2. Stabilized tubulin mRNA and increased protein levels	200, 201
Human CNS and NSC	Proliferation and differentiation of multipotent neural stem cells and prevention of apoptosis, Aβ toxicity, oxidative stress, and ischemia	1. Prevented apoptosis through PI3K pathway, but via MAPK pathway 2. Protected cells against Aβ-induced cell apoptosis	202, 203
Extrasynaptic space	Induction of GABA and glutamate accumulation	1. Elevated neuronal antioxidants such as uric acid, glutathione, and vitamins C and E 2. Altered glucose metabolism and decreased lactic acidosis	204, 205
Hippocampus	Anti-ischemic effect	Stimulated Na^+/K^+ ATP pump to reduce extracellular K^+ and intracellular Na^+ to change neuronal firing rate and its metabolic demands	
Rat hippocampus	Anti-ischemic effect	1. Induced Akt and JNK1/2 cross-talk 2. Reversed induction of JNK1/2 phosphorylation, Bcl-2 expression, and caspase-3 cleavage	8
Hypothalamus	Alteration of intracellular ion concentrations	1. Stimulated Na^+/K^+ ATP pump 2. Increased intracellular Ca^{2+} concentration triggering neuropeptide release	70
Hypothalamus	Modulation and stimulation of aminoacid uptakes, neurotransmitter receptor density and synthesis	1. Reduced the increase of striatal dopamine receptor numbers and CSF serotonin levels 2. Downregulated α_2-adrenergic receptors in the hypothalamic neurons	206, 207
Hypothalamus synapses	Modulation of glutamatergic neurotransmission at the synapses and induction of LTD process by reduction of AMPA receptor levels in the postsynaptic membrane	1. Phosphorylation of the hormone receptor, PI3-kinase activation 2. Induced GluR2 subunit phosphorylation in the AMPA receptors to produce endocytosis and decrease of postsynaptic excitatory ability	208, 209
CNS	Induction of GABA receptor effects on learn and memory processes	1. Stimulated GABA receptor translocation to plasma membrane 2. Abolished by PI3K inhibitor 3. Increased expression of functional GABA receptors on the postsynaptic and dendritic membranes of CNS	210–212
CSF	Induction of tyrosine, tryptophan azidothymidine, and leptin transportation from blood to the brain	Induced P-gp expression involved in the BBB integrity and protects brain against numerous exogenous toxins	213
Brain microvessels	Induction of neurochemical modifications in the brain microvessels	1. Inhibited alkaline phosphatase activity 2. Increased expression and activity of glutamate–cysteine ligase catalytic subunit by inducing antioxidant response element-4	8, 214, 215
Choroid plexus	Inhibition of serotonin receptor 5-HT2C receptor activity	Modulated GPCR by tyrosine kinase receptor–MAP kinase pathway	

Abbreviations: Aβ, β-amyloid protein; AD, Alzheimer's disease; BBB, blood–brain barrier; CNS, central nervous system; CSF, cerebro spinal fluid; GABA, gamma-amino butyric acid; LTD, long term depression; MAPK, mitogen-activated protein kinases; mTOR, mammalian target of rapamycin; NGF, nerve growth factor; NSC, neural stem cells; PI3K, phosphoinositide-3-kinase.

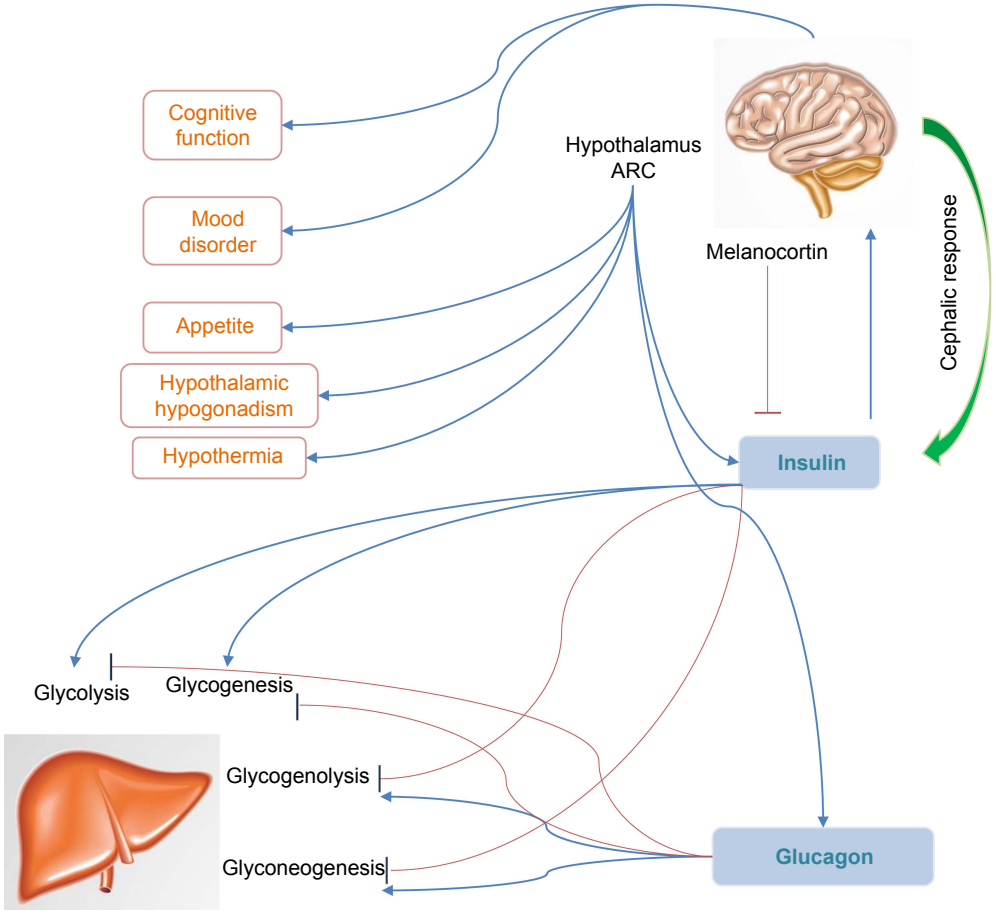

Figure 1 Regulation of carbohydrate and fat metabolism, mediated by insulin hormone in the brain, on central and peripheral functions.
Notes: Regulation of carbohydrate and fat metabolism is mediated by insulin through increasing the transport of glucose from the blood to fat tissue and skeletal muscles. Disturbance in the insulin levels in the periphery system leads to diabetes, but in the brain develops certain neurodegenerative states such as AD.
Abbreviations: AD, Alzheimer disease; ARC, arcuate nucleus.

and up to seven IGF-binding proteins (IGFBP1-7).[28,29] IGF-1 and insulin can control the neuronal excitability, metabolism, and survival through insulin/IGF-1 signaling pathway. Abnormality and disruption in the activity of these pathways trigger the continuous dwindle of neurons in AD brain.[30,31] Few evidences on the brain of AD patients showed deficit ratio of insulin and resistance in IGF-1, suggesting that AD might be a brain-type diabetes or diabetes type 3.[32,33] Altered neuronal IGF-1 function seems to be an important aspect of the overall synaptic and neuronal pathology induced by Aβ protein precursor (AβPP)-Aβ clearance in the apoE4 carriers. Hence, both hyperinsulinemia and hyperglycemia can increase the neuritic plaque formation and progress in AD.[30,34]

Energy expenditure

The amount of energy which is consumed for the performance of physical activities, such as inhalation and exhalation, blood circulation, breakdown of food particles, or physical movement, is known as energy expenditure. This energy is obtained by the electrochemical gradient generated by the electron transport chain (ETC) which drives ATP synthesis via ATP synthase. The ATP production capacity and/or efficiency is performed via mitochondrial dynamics in beta cells.[35,36]

Leptin as an adipocytokine which is produced in the peripheral system as well as in the brain possesses key role in phenomena such as food intake, obesity, glucose homeostasis, and energy expenditure. It is proved that both leptin expression levels and signaling pathways could be connected to the pathophysiology of many neurodegenerative diseases, such as AD. It is illuminated that leptin receptors are highly expressed in the hippocampus involved with learning and memory, and are found critically affected in AD patients. In vivo and in vitro studies suggest that leptin supplementation could decrease both Aβ production and tau phosphorylation which contribute to the development process and pathogenesis of AD.[37] Insulin secretion occurs in blood stream based on the availability of free fatty acid, amino acid, and beta cell measures glucose through mitochondrial

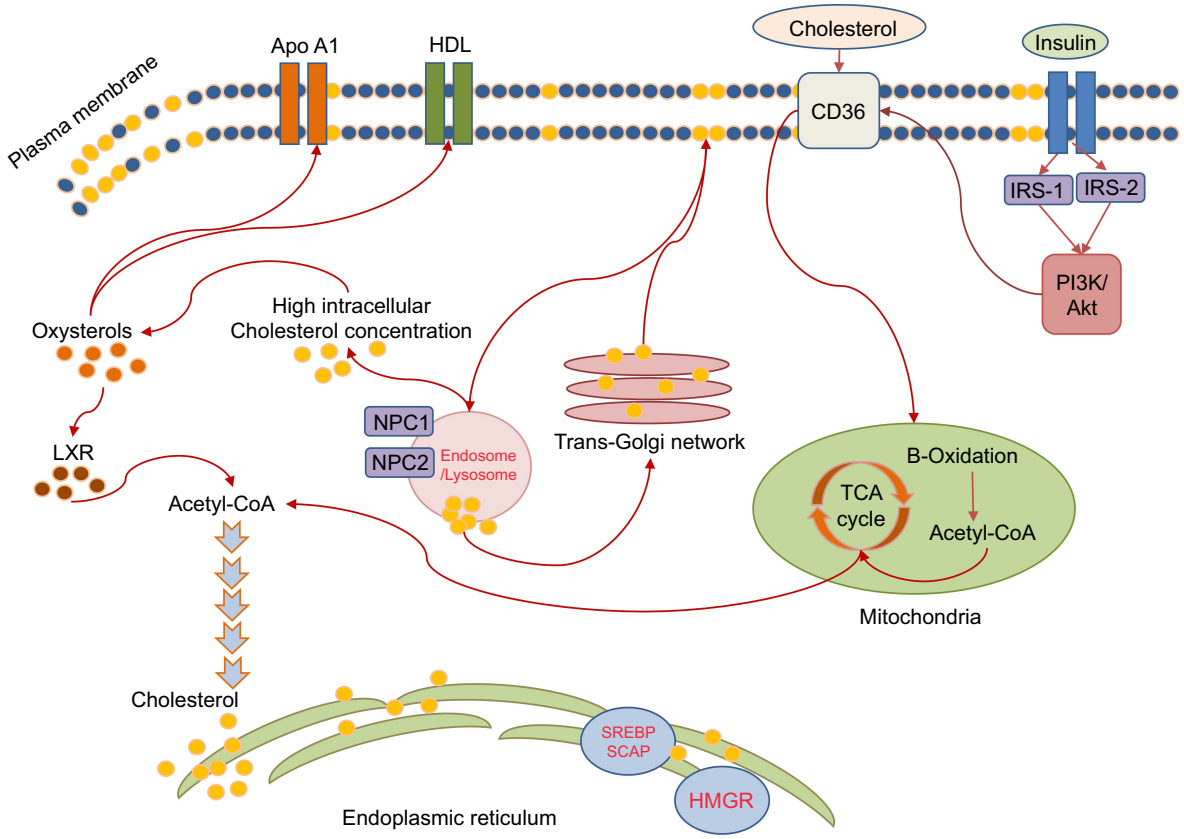

Figure 2 Crucial role of cholesterol in membrane.
Notes: Cholesterol is imported through receptor-mediated endocytosis of lipoproteins and through lysosomes and transported to the cell membrane. Thus, it causes the interruption on brain cholesterol metabolism, thereby leading to neurological disorders.
Abbreviation: PI3K, phosphoinositide-3-kinase.

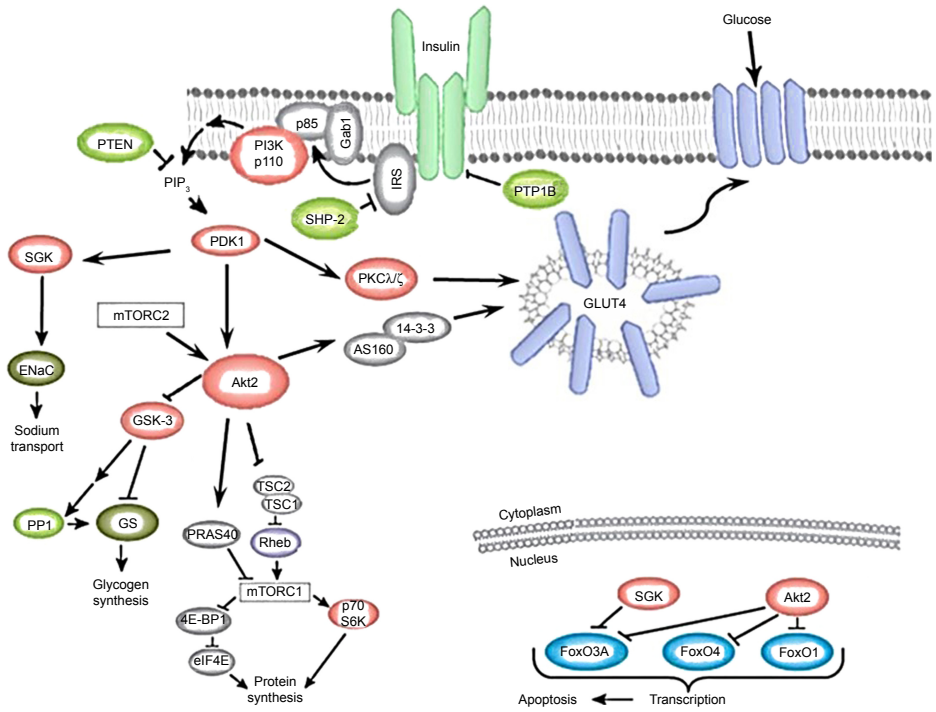

Figure 3 Glucose uptake eventually occurs through translocation of GLUT4 to plasma membrane.
Notes: Any damage in the underlying mechanism of GLUT4 protein action in the hippocampus affects the chemical reactions and cognitive flexibility provided by hippocampal neurons; this condition develops depression and lowers the cognitive function, consequently increasing the risk of Alzheimer development. Reproduced from Hajiaghaalipour F, Khalilpourfarshbafi M, Arya A. Modulation of glucose transporter protein by dietary flavonoids in type 2 diabetes mellitus. *Int J Biol Sci.* 2015;11(5):508–524.[240]

respiration and nutrient oxidation accordingly. The main stimulator of insulin secretion signal is elevation of cytosolic ATP/ADP ratio or high glucose oxidation, mitochondrial ATP synthesis, and low ATP demand in the beta cells.[38,39] Permanent excess nutrient or continuous exposure to fat in T2DM damages mitochondria or decreases its function in the beta cell through reduced antioxidant activity and sustained overproduction of reactive oxygen species (ROS), independent of changes in mitochondrial ATP synthesis.[40] Besides, NF-κβ, TNF-α, and IL-6 as acute inflammatory cytokines lead to negative energy balance and promote energy expenditure and increase ROS.[41,42]

It is shown that abnormal production of AT-derived proteins contributes to the pathogenesis of insulin resistance and metabolic syndrome such as T2DM.[9,43] The inflammatory cytokines elevation, energy expenditure, and insulin deficiency result in high glucose expenditure and accumulation of β-amyloid peptide as a hallmark of AD.[8,9,28]

Role of leptin in glucose homeostasis

A balance between the insulin and glucagon maintains blood glucose levels or glucose homeostasis. Insulin exerts its pleiotropic effects through binding to the insulin receptor substrate (IRS) proteins which mediate regulation of glucose transport, protein metabolism, and control of cell growth and survival. IRS proteins connect insulin receptor activation to essential downstream kinase cascades, such as the phosphoinositide-3-kinase (PI3K) or mitogen-activated protein kinases (MAPK) pathways. Decreased IRS-1 contributes to reduction of glucokinase and increases blood glucose levels in diabetes.[44–46]

As we know, hypothalamus regulates leptin signaling that has a role in food intake and energy homeostasis in mammals which results in the downregulation of orexiogenic peptides, such as neuropeptide Y (NPY) and agouti-related peptide (AgRP), and in reverse, it can increase the expression of anorexiogenic peptides, such as α-MSH, which promotes energy expenditure in either adipose or skeletal muscle tissue. It is indicated that leptin-mediated ObRb receptors are expressed in vast density in the arcuate nucleus (ARC), dorsomedial nucleus (DMH), and the ventromedial nucleus (VMH) of the hypothalamus. In the ARC, obRb is rarely expressed in two different neuronal cell types of the hippocampus (CA1 and CA3 regions) and the dentate gyrus,[47] which express both NPY and AgRP, and proopiomelanocortin (POMC) is mainly expressed.[48,49] Also, leptin increases synaptogenesis and aids in memory formation in the hippocampus and is pretended to be a cognitive promoter.[50] Similarly, it was shown to elevate neurogenesis in the dentate gyrus in rodents.[51] Leptin also plays a vital role in hippocampal neuronal survival via activating the PI3K/Akt/mammalian target of rapamycin (mTOR), as well as the AMP-activated protein kinase (AMPK)/SIRT1, JAK2/STAT3, ERK pathway signal transduction pathways through binding to its long-form receptor obRb.[52] Leptin upregulates the expression of some potent endogenous antioxidant enzymes involved in apoptosis, such as manganese superoxide dismutase and the anti-apoptotic protein Bcl-xL in the hippocampus.[52]

Leptin can modulate Aβ production and metabolism. Interestingly, chronic peripheral leptin administration in Tg2576 mice reduced tau phosphorylation explicitly at residues Ser202, Ser396, and Ser404 in retinoic acid. Such reduction is suggested to be mediated via AMPK, Akt, and p38 pathways.[53,54] All these evidences could illuminate the role of leptin in T2DM and highlight AD linkage. Moreover, epidemiological studies have also found depleted leptin levels in the pathogenesis of AD. In a study by Narita et al, it was found that higher leptin levels positively correlate with higher hippocampal volumes.[55] It should be noted that all the leptin-induced signaling pathways link to phosphorylation of glycogen synthase GSK3β and decrease in hyperphosphorylation of tau.[56] It is interesting that the low circulating leptin levels, in turn, could potentially contribute to cognitive decline and worsen the pathology, leading to a downward spiral of further weight loss and progression of AD.[57] The presence of amyloid plaques, NFTs, and neurodegeneration in the hypothalamus of human AD brains suggest that Aβ-mediated suppression of leptin-responsive cells in the hypothalamus is extremely possible.[58,59] Hence, leptin may possess a bidirectional role in the dysfunction of leptin signaling that exacerbates AD pathology.

In addition, insulin activates PKB (or Akt) which is a serine/threonine kinase, composed of various members, including PKBα (Akt1) and PKBβ (Akt2). Only PKBα drives islet and β-cell proliferation. Interestingly, PKBα-deficient mice also revealed normal insulin-stimulated disposal of blood glucose.[60,61]

TNF-α is a key cytokine that influences intermediary glucose metabolism which compromises IR/IRS-1 signaling independently of transcriptional regulation. This effect is mediated by minimum of seven serine kinases, which include c-JUN-NH_2-terminal kinase (JNK), Akt/PKB, and IKK. Tyrosine phosphorylation of IRS-1 and IRS-2 serine at 307 residues is an essential factor to actively downstream effector pathways impairment in the insulin homeostasis.

Insulin homeostasis impairment affects glucoregulatory mechanisms characterized by altered glucose tolerance and causes insulin resistance leading to escalation of Aβ peptide, APP, NFTs neurotoxicity, and tau phosphorylation associated with AD.[8,61,62]

Feeding behavior

Controlling the body mass by maintaining food consumption underlies a twisted flow. Excess of food intake contributes to the onset and progression of the metabolic syndrome. Some hormones such as insulin, glucagon-like peptide 1 (GLP-1), and leptin are involved in the regulation of food uptake and energy consumption.[63–66] Insulin with leptin exerts their acute effect by altering cells' function and nutritional behavior via PI3K pathway. PI3K increases α-MSH release and decreases NPY release which induces depolarization of AgRP neurons and increases food intake. GLP-1 also regulates glucose homeostasis and reduces food intake. Food intake and the anorexic brain-gut peptide GLP-1 activate amygdala dopamine signaling through D2 receptor which is necessary and sufficient to alter the feeding behavior.[67–69]

Hypothalamic AMPK regulates food intake as well as body weight through altering the expression of NPY, AgRP, POMC, and CART in the ARC nucleus. Unlike feeding, fasting increases hypothalamic AMPK activity. In the hypothalamus, minimum of two mechanisms exert impact on the anorexigenic effects on AMPK inhibition which results in the activation of acetyl-CoA carboxylase (ACC) and mammalian target of rapamycin (mTOR), and the phosphorylation of p70S6 kinase (p70S6K).[68–71] In T2DM, increased mTOR and p70S6 kinase expressions elevate production of leptin which has direct effects on food intake. Feeding behavior dysfunction in T2DM modulates brain functionality leading to neurodegeneration process such as AD through overproduction of APP, Aβ 1–42, and thereby accumulations of Aβ, and also contributes to NFTs production.[2,72]

Synaptogenesis feeding behavior

Synaptogenesis is a multi-step process of synapse formation which is promoted by IGF-1 and IGF-2 through several pathways during all the major phases of neurodevelopment. The activation of protein kinase C (PKC) also regulates synaptogenesis through phosphorylation, binding to signaling lipids, and translocation from the cytosol to the membrane.[17,29,73–75] Phosphorylation of PKC at the first step is essential for its activation and formation of its catalytically active competent conformation. PI3K activation by insulin also induces synaptogenesis and controls the expression of synaptic markers in addition to their accumulation in the nerve cells. PI3K, accompanied with the existing elements of the InR signaling pathway, controls cellular magnitude, growth and multiplication, and creation of synapses in between the neurons. PI3K and B/Akt protein kinase regulate the development of synapses as well as their preservation. PI3K acts via its binding to synapsin, actin filaments, and high phosphoinositide levels that are linked to the cAMP pathway and cAMP response.[60,76] The sites of expression of IRSp53 in the synapses are located on the granular layer of the cerebellum and hippocampal neurons, which suggests that these molecules are components of insulin-dependent signaling pathway at the postsynaptic apparatus. IRSp53 is a key factor in cytoskeleton which is phosphorylated upon stimulation with insulin and involved in neurite outgrowth and neurodegenerative disorders.[8,77] Insulin stimulates translation, but not the transcription, of postsynaptic density PSD-95 in the hippocampal CA1 neurons, through the PI3K–Akt–mTOR pathway, an important intracellular signaling pathway in regulating the cell cycle.[74,78] There is a linkage between the phosphorylation of IGF1-induced Akt and release as well as the translocation of GLUT4 from intracellular pools to nerve process membranes in the normal developing brain. High glutamate levels phosphorylate the Ser (307) residue in the IRS-1 protein which develops less reactivity and induces IGF-I via activation of pathway associated with protein kinase A (PKA) and PKC. This action arises due to a reciprocal activity between IGF-1 and nerve growth factor (NGF) in the peripheral nerves, where the PI3K/Akt/GSK3 pathway underlies the impact raised from the cooperation of both agents on axonal growth. Insulin signaling pathways activate PKC and its substrates, many of which are vital components of synaptogenesis, cognition and neuronal repair, differentiation, growth, and apoptosis.[79]

Insulin also activates MAPK pathway through tyrosine phosphorylation of certain prototypical signaling adaptors such as Shc/Grb2, SOS/Grb2, and Gab-1/Shp2. Diabetes declines the activity of PI3K/AKT/mTOR in the enteric neurons, which impairs retrograde NGF transport in the vagus nerve. Activation of PI3-phosphatase decreases cellular contents of lipid products by PI3K. Any defects in the intracellular PI3K translocation or phosphatase activation may modify Akt/PKB activity.[74,78,80] Synaptogenesis and synaptic remodeling increase Aβ oligomers which can directly produce neuronal insulin resistance and directly bind to PKC and inactivates it. GSK-3β phosphorylates multiple sites of tau protein in the intact cells. Aberrant hyperphosphorylated tau protein is a critical feature in AD pathogenesis

that signifies a close molecular relationship between diabetes and AD.[74,80,81]

Neurotrophy

Neurotrophy or nerve damage is strongly regulated by insulin which is essential for neuronal development and survival via IGF-1 and ROS signaling pathways. IGF-1 pathway coordinates growth, proliferation, differentiation, development, metabolism, and glucose homeostasis. The graft of IGF-1 and the related receptor trigger the phosphorylation of essential adaptor proteins together with Shc and IRSs, which leads to the activation of two prosurvival signaling pathways.[75,82,83] Phosphorylation of IRS-1 or IRS-2 stimulates PI3K–PDK1–AKT signaling pathway, whereas phosphorylation of Shc induces RAS, RAF, and ERK/MAPK signaling pathway which leads to regulation of neurotrophy. Moreover, phosphorylation of threonine 308 via PDK1 or phosphorylation of serine 473 via mTORC2 results in the activity of AKT; this activation increases the life span of cells through abundant mechanisms, like deterrence of apoptosis and giving rise to prosurvival gene expression. Decreased levels of serum IGF-I in DM patients with sensory and autonomic neuropathy compared with nonneuropathic DM or nondiabetic controls and IGF-I and IGF-II lead to sympathetic neuroaxonal dystrophy. IGF-1 blocks amyloid toxicity by increasing survival signaling through PI3–AKT and ERK which accumulate high levels of Aβ from overexpressing APP. The Aβ oligomers elevate pro-inflammatory cytokines in the brain that mimic the trophic factor/insulin resistance as observed in AD brain.[18,30,71,75,84]

Apoptosis

Several studies suggest the protective role of insulin against apoptosis through various signaling pathways that suppress the excessive accumulation of ROS within the cells.[85] The insulin/IGF/Akt is one of these pathways in promoting β-cell survival. However, ER stress–induced apoptosis is mediated at least in part by signaling through the phosphatidylinositol 3-kinase/Akt/GSK3β pathway. Moreover, presence of advanced glycation end products (AGEs) and advanced lipoxidation end products (ALE) that merely resulted from a long-term accumulation of modified protein can be considered as a stress. Chronic hyperglycemia-induced OS such as nitric oxide (NO) plays a central role in the formation of AGEs in DM.[86,87] G-protein-adenylyl cyclase signaling, diacylglycerol (DAG)/PKC pathway, and calcium movement play a vital role in diabetes-induced galactooligosaccharide (GOS). Normalization of mitochondrial superoxide production blocked AGEs overproduction, PKC activation, and increased glucose flux through the aldose reductase pathway and NF-κB activation.[88,89]

Impaired immune system in diabetes is almost affiliated with the reduction of antioxidant activity and antioxidant enzymes manifestation as well as eccentric performance or abnormal enzyme activities. Among the diversity of the existing antioxidant enzymes, SOD, GPx, and CAT reflect greater impact on the regulation of ROS formation and entire antioxidant content available in a certain tissue as well as in DM.[90–92] NADPH oxidase and dysfunction of mitochondrial respiratory chain (MRC) are also a major source of ROS in diabetes. Thus, blocking the overexpression and activation of this enzyme and subsequent ROS production together with its ROS scavenging property reduce OS in diabetes. Mitochondrial-derived superoxide anion is common in complications with diabetes. Overexpression of manganese-dependent superoxide dismutase (Mn-SOD), which is the major scavenger of mitochondrial superoxide anion and mitochondrial DNA damage in T2DM, prevents high glucose-induced OS and cell apoptosis. OS-related pathways interconnect AD and T2DM. It is a well-known connection of Aβ protein and hyperphosphorylated tau with glucose metabolic intermediates and IRs. Insulin transporters cause this interconnection in the AD brain, Aβ accumulates in the plaques, and receptor for AGE mediates Aβ 1–42-induced perturbations of APP and NFTs neurotoxicity (Figure 4).[18,87,89,93]

Neurotransmitters

Endogenous chemical messengers that enable transmission of signals from one neuron to the target neuron, muscle cell, or gland cell stimulating insulin and glucagon are demarcated as neurotransmitters. Glutamate is one of the most abundant neurotransmitters in the brain; an excess of glutamate overstimulates brain cells, which results in neurological inflammation and cell death. A high glutamate concentration triggers insulin release to lower glucose levels which in turn increases glutamate. Another neurotransmitter, gamma-amino butyric acid (GABA) in the CNS, prevents nerve transmission in the brain and has a calming nervous activity. Heavy secretion of insulin results in a protracted secretion of GABA, glutamate, aspartate, and taurine through the number of $GABA_A$ receptors. Moreover, insulin therapy could be considered as an efficient therapy to bridle the toxic activity of neurotransmitters to preserve neurons. Therefore, there is a close linkage between GABAergic signaling system and various aspects of AD pathology, including tau hyperphosphorylation, Aβ toxicity, and apoE4 effect. Low levels

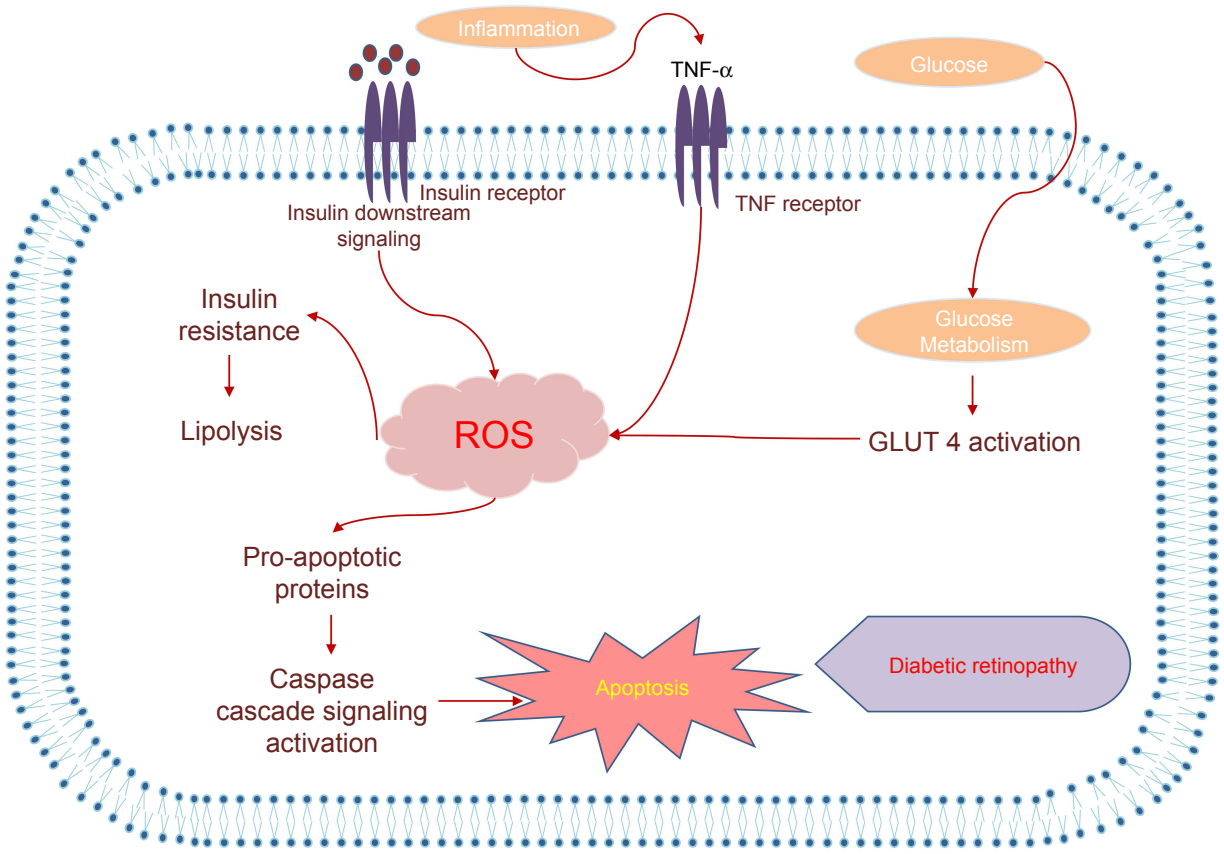

Figure 4 The protective role of insulin against apoptosis through various signaling pathways to suppress the excessive accumulation of ROS within the cells results in early diabetic retinopathy.
Abbreviations: ROS, reactive oxygen species; AGE, advanced glycation end product; PEDF, pigment epithelium-derived factor.

of GABA and glutamate cause significant limitation in the activities of synapses and synaptic transmission of neurons in the temporal cortex of AD patients, and activation of $GABA_A$ receptors induces tau hyperphosphorylation.[18,94–96]

Promoting glycogen synthesis

Synthesis of glycogen from glucose in skeletal muscle is regulated via the activity of certain hormones such as insulin. Muscle and liver uptake the available glucose upon stimulation by insulin hormone and leads to the activation of glycogen synthase (GS) through dephosphorylation of three specific serine residues, collectively termed sites 3.[97–99]

GS kinase (GSK)-3 is principally responsible for phosphorylation of sites 3, whereas phosphatase (PP)-1, a glycogen-bound form of protein, dephosphorylates these sites.[100] However, defeat in tracing the fall in quantity of cAMP localization in muscles is associated with a secondary glycogen synthase kinase which is not influenced by cyclic nucleotides. Immediate effect of insulin is to redirect synthesized glucose-6-phosphate to glycogen without affecting the rate of gluconeogenesis which requires hepatic Akt2-dependent redirection of glucose-6-phosphate to glycogen independently of GSK3α and GSK3β phosphorylation. Downstream defects at the level of glycogen synthase kinase (GSK)-3 or impaired regulation of the GSK3 target site of GS (site 3a/b/c and 4) which leads to abnormal phosphorylation in activation of GS and dysregulation of CaMKII seems as a major cause of insulin resistance phenomenon. In AD brain, increased activities of Akt, PKA, and GSK3α, and β and Aβ-induced GSK3β phosphorylation increase tau phosphorylation which leads to mitochondrial dysfunction.[99–102]

Cognition and memory

Controlling the transmission of ions through neuroreceptors located on the membrane is activated by neurotransmitters and synaptic transmission which influence the cognitive function in the presence of insulin.[77] Suppression of Wnt or PI3-kinase signaling ruin the synaptic connections between neurons which is known as long-term potentiation (LTP) and results in the less synaptic strength which affects the process of learning and memory function. GSK3β at high expression level suppresses LTP impact, thus providing lesser spatial learning.[103,104] GSK3 also phosphorylates and inhibits cAMP-responsive element-binding protein, a universal modulator

of memory.[105] Moreover, GSK3 promotes actin and tubulin assembly, processes required for synaptic reorganization during memory formation. PI3K/Akt/GSK-3β is another pathway to impair the ability of insulin in activation of glucose disposal and glycogen synthase in T2DM. Overexpression of GSK3 induces a series of pathological changes, most of which are hallmarks of AD and T2DM incurring severe pathology, such as cognitive decline. Adiponectin is an important target for AD by induction of Aβ and Tau phosphorylation in hippocampus and extrahypothalamic region. GSK3β together with GSK3α causes AD by inducing tau hyperphosphorylation to form NFTs through PI3K/Akt/GSK-3β signaling pathway.[103,106–108]

Inflammation

Insulin suppresses the pro-inflammatory proteins such as JNK, IKKβ/NF-κB, AP1, CAM1, PSD95, and MCP1 which downregulate the inflammatory response. Inflammation together with insulin resistance is increased by expression of several pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α. In contrast, IKKβ acts selectively against the physiological substrates and the IκB protein inhibitors of NF-κB. Phosphorylation by IKKβ targets IκBα to degrade proteasome that liberates NF-κB for translocation from cytoplasm into nucleus to promote expression of numerous target genes and consequently induce insulin resistance.[42,62,109–111]

PI3K–Akt–mTOR signaling pathway facilitates the synthesis of PSD-95 protein via insulin induction in Dendron's and hippocampal area. PSD-95, a 95-kDa scaffolding protein of PSD, is degraded by IL-1β. T2DM enhances pro-inflammatory factors in the brain cells such as microglia and astrocytes that contribute and provoke AD. Inflammatory agents like toxicants and pollutants when accumulated in higher proportion lead to cellular stress, amyloid precursor protein (APP), and rise in genesis state, thereby stimulating amyloid-β–42 (Aβ–42) peptide production.[78,112]

Role of insulin resistance and tau protein in AD

Insulin resistance, impaired glucose tolerance, and formation of insoluble protein aggregates, as well as the loss of neurons and synapses, extend risk factors in the development process of AD, but evidence for this assertion is not consistent. Impaired insulin signaling certainly does not preclude evidence from having a deficit effects on cognition independent of its role in AD pathology, such as diminished learning, memory, problem solving, and mental flexibility. Mechanisms of T2DM progression to AD by insulin are classified into two main categories: NFTs and Aβ formation. Various experimental paradigms suggest that Aβ and tau have been found to exert synergistic modes of toxicity, while the effect of insulin on the brain is complex and not confined to Aβ production (Figure 5).[2,9,18,113,114] Tau protein plays a wider role in cellular shape, motility, and signal transduction in AD. The C-terminal of this protein is probably responsible for tubulin-binding and the acidic N-terminal region interacts with other cytoskeletal elements. The proline-rich middle region contains the target sites of many kinases. Moreover, R1–R4 are four repeat domains called microtubule-binding domains (MBDs) and each of them repeats and conserves consensus motif KXGS, which can be phosphorylated at serine.[115,116]

Insulin can modulate phosphorylation of tau protein which are MBD molecules involved in microtubule assembly and stabilization. Dysfunction of insulin can cause tau hyperphosphorylation through two different mechanisms at specific amino acids including Ser and Thr: glucose/energy metabolism and temperature independent.[117,118] Out of 85 phosphorylatable residues in tau protein, 28 sites are exclusively phosphorylated in AD brains (Table 2). Reduced insulin plasma levels in T2DM can impair this signaling pathway resulting in tau hyperphosphorylation and disintegration of microtubules and thereby formation of NFTs.[115] Most promising candidate kinases for tau phosphorylation which are responsible to provoke AD and T2DM are listed in Table 2. The details and the functions of each kinase are as follows:

GSK3β

It was shown that H_2O_2 increases GSK-3β activity in human embryonic kidney 293/Tau cells which leads to tau hyperphosphorylation at Ser396, Ser404, and Thr231. GSK3β is involved in the formation of both Aβ deposits and NFTs, two pathological features of AD. The Aβ promotes GSK-3β activity in the neuronal cells which is at Thr231 residue, but it enhances phosphorylation at the S9, S68, T69, T71, T175, and Ser396/404 sites which decreases tau–microtubule interactions and the pathologic fibril formation, thereby reducing tau binding to microtubules.[119–122]

c-JUN-NH_2-terminal kinase

The JNK is a subfamily of the MAPK that binds and phosphorylate c-Jun on Ser-63 and Ser-73 within its transcriptional activation domain. The β2-adrenergic receptor (β2AR)–PKA–JNK pathway phosphorylates tau protein at Ser-214,

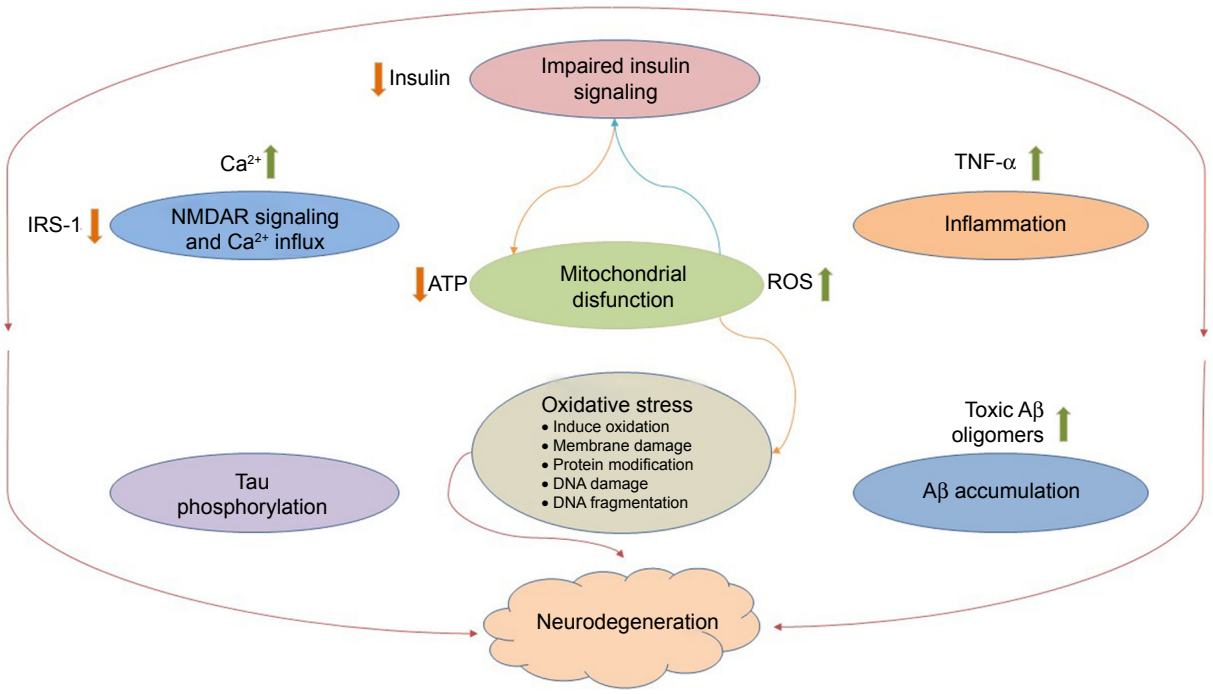

Figure 5 Glucose tolerance and DM are the syndromes in the elderly and there is evidence in supporting a link between insulin dysfunction and AD.
Abbreviations: AD, Alzheimer disease; DM, diabetic mellitus; ROS, reactive oxygen species.

Ser-262, Thr231, and Thr-181, which are utilized by Aβ signals in the primary neurons of prefrontal cortex (PFC) in mouse brain.[123] Knocked-out β2AR mice showed an extreme decrease of phosphorylation of presenilin 1 (PS1) and APP associated to the Aβ-induced tau pathology in AD. Aβ also induces the clusterin/p53/Dkk1/wnt–PCP–JNK pathway, which drives the upregulation of several genes that mediate development of AD-like neuropathologies; these studies are in agreement with the animal experiments.[124]

JNK plays a critical role in regulation of insulin signaling, inflammatory response, apoptosis, and caspase-3 activity in diabetes and increases the expression of IL-6, IL-8, monocyte chemotactic protein-1, and tumor necrosis factor-α 35 in AD pathology.[8,125,126]

CamKII

Calcium-/calmodulin-dependent protein kinase type II is one of the abundant Ca^{2+}-regulated protein kinases in the brain; these kinases are expressed primarily in neurons. CaMKII is regulated by Ca^{2+}-/CaM-induced autophosphorylation at multiple sites such as Thr 286/287.[127] The tau phosphorylation is upregulated at Ser214, Ser262, Ser131, Thr212, and Thr135 by CaMKII kinase in frontal cortex and hippocampus, and is found in PHF-tau of AD brains and T2DM which leads to the inactivation of protein phosphatases (PP).[118,128] Obviation of synapses results in depleting the memory function in preliminary stage of AD which is expected to be induced via Aβ oligomers by CaMKII. *O*-GlcNAc modification by CaMKII at Ser 279 activates CaMKII autonomously, creating molecular memory even after Ca^{2+} concentration declines in T2DM.[129] Furthermore, it was shown that the activation of CaMKII directly inhibits AGEs formation significantly and reverses D-ribose-induced tau hyperphosphorylation which links T2DM to AD.[115,128]

CDK5

Cdk5 belongs to the Cdk family which is expressed in the CNS and other tissues. It regulates several cell processes such as neuronal migration, actin, and microtubule dynamics. Cdk5 acts through PP1 and regulates several proteins such as inhibitor-1 (I-1) and I-2. P25 is a neurotoxic activator of cdk5 which triggers tau phosphorylation and NFTs formation in AD pathophysiology.[130] Moreover, p35 is a neuronal-specific protein that is nonhomologous to cyclins, and is responsible for the identification and activation of Cdk5 in association with Cdk5R1 or Cdk5R2. Interestingly, the study on gene-targeted therapy opens up the clue with potential role of p35/Cdk5 kinase in the migration process of neurons as well as in the development stage of mammalian cortex.[131] Expression of Cdk5 and its co-activator p35 is upregulated in the presence of high glucose concentration and strong bounding with Cdk5 kinase is

Table 2 Progression of diabetes to AD, the molecular cascade involving the function of insulin in the brain: the enzymes which are activated in diabetes type 2 could phosphorylate the specific Tau residues leading to ADs

Kinase	Residue(s)	Alzheimer's linked phosphorylation	Ref
GSK3β	S68, T69, T71, T175, S235	Leads to Thr231 phosphorylation and consequent pathologic fibril formation, inhibits the ability of tau to stabilize microtubules and cell death	119–122
GSK3β, Dyrk1a, JNK, MAKR, p38 (MAPK)	T181, S63, S73	Leads to early events in NFT formation and deregulating tau–microtubule interactions and indicative of the presence of pretangle tau	121, 216
PLK2	S129	• Inhibits the α-syn-induced tau mass to form intracellular neurofibrillary tangle-like aggregates • Upon investigation of phosphorylation spots, it was found that numerous factors including glycogen synthase kinase 3 beta or MAP/microtubule affinity-regulating kinase 2 may be associated with this effect	153, 217, 218
Syk/Fyn	Y18	• Leads to congregation of microtubules and their solidity along with its involvement in the formation and preservation of neuronal polarity • Hypophosphorylation of Y 18 has the role in neurodegeneration • The reciprocal action between direct Syk and α-syn was proven by a dual-hybrid system approach and confocal microscopy • To be involved in neurons cell-signaling pathway	154, 219
GSK-3 Syk/TTK1	S191 Y197	• Leads to abolishing the microtubule-stabilizing effect which is observed in tau-transfected cells • In immature neurons, S191 phosphorylation may favor the microtubule dynamics which is probably required for neurite growth • The aberrant hyperphosphorylation of tau in AD may shift the balance toward excessive microtubule • Leads to defective axonal transport of organelles and impaired retrograde axonal transport of neurotrophic factors as well as to alterations in neurite morphology	220–222
Cdk5, PKA, GSK-3, Dyrk1a, JNK, MARK, p38, CK1	T175, T181, S184, S195, S198, S199, S202, S235, S356, S396, S400, S404	• Prevent pathologic tau fibril formation and develop pathologic tau fibrils, and thus indicating a potential therapeutic avenue for amyotrophic lateral sclerosis with cognitive impairment • Leads to physiological role of microtubule dynamics regulator, whereas another set (overlapping or not with the previous one) leads to aggregation into PHFs, degradation, and/or toxic function • Leads to detachment of tau from microtubules • Leads to the formation of a linkage between p-p70S6K (T421/S424) and S262 or S396/404, by facilitating site-specific phosphorylation on regulatory (T389) and catalytic (T229) domains • A raise in the function of 70S6K might be possible, which in turn may phosphorylate tau at T212, S214, and S262 sites • Leads to attachment with some proteins such as PP-1, actin, PP-2A, phospholipase C, α-synuclein, and glycogen synthase kinase-3β which is related to AD	121, 122, 161, 190, 223, 224
Cdk5, CK1, PKA, GSK-3, PKB/Akt	S214	• Leads to suppress tau-dependent microtubule polymerization and inhibit axonal elongation in neurons • Leads to reduce its ability to bind to microtubules • To have some effects on microtubule association on tubulin, the tau-interacting site is located at the carboxyl terminal end, which is highly acidic and detaches from microtubules • Leads to reductions of the tau–microtubule interaction in vitro • Leads to suppress microtubule assembly, and may be a key factor in the observed detachment of tau from microtubules during mitosis	223, 225, 226
GSK3β, Cdk5	S202, T205	• Leads to microtubule dynamics regulatory • Leads to detachment of tau from microtubule	227–229
Cdk5, PKA, CK1, GSK-3, PKB/Akt	T212, T214, T262	• Level of (70-kDa p70 S6 kinase) p-p70S6K (T421/S424) is only significantly correlated with p-tau at T212, S262, and S214, but not at T212/S214, in AD brains. These suggested that p70S6K might contribute to tau-related pathologies in AD brains • Leads to compromise its binding ability to microtubules • Phosphorylation of protein tau at the S262 site perhaps leads to the suppression of microtubule clustering and their stabilization. However, T212 site did not express a significant potency to assemble microtubules; prephosphorylation at this site has been shown to enhance S214 phosphorylation	119, 121, 123, 154, 216, 228, 230

(*Continued*)

Table 2 (*Continued*)

Kinase	Residue(s)	Alzheimer's linked phosphorylation	Ref
		• Ps262 leads to microtubule-binding repeat domain which can be detached from the microtubules and may thus be protective in preventing tau aggregation into AD-like PHFs • Perhaps, the phosphorylation of tau at T212 and S214 sites result in the neutralization of the fundamental charges, followed by the neutralization of inhibitory effect of S262 phosphorylation that causes tau to self-assemble into filaments • Leads to the disconnection of microtubules and blockage of PHF formation in degenerating neurons in AD • Leads to reduce its ability to bind to microtubules • Leads to detach from microtubules • Leads to strongly decrease the tau–microtubule interaction in vitro • Leads to inhibition of microtubule gathering and might induce detachment of tau protein from microtubules during mitosis	
GSK-3, Cdk5, PKA Dyrk1a, JNK, MAPK	T231	• Prevents pathologic tau fibril formation, regardless of Thr^{175} state and develop pathologic tau fibrils • Leads to fibril formation, indicating a potential therapeutic avenue for amyotrophic lateral sclerosis with cognitive impairment • Leads to less binding potency microtubules via the activity of Ras–MAPK pathway • Pin1 interacts only with phosphorylated T231; this connection evolves a conformational alteration resulting in the attachment of tau protein to microtubules	121, 122, 216, 228, 231, 232
GSK-3, Cdk5, PKA, Dyrk1a, JNK, MARK	S262, S393, S324, S356	• Prevents the binding to microtubules 115 and aggregate into PHFs • Leads to destabilizing microtubule assembly; functions and localizations of other subcellular structures such as mitochondria and lysosomes could be altered • Leads to exert itself toxic effect on microtubule binding, and can lead to the breakdown of the microtubule network and cell degeneration • Appears to play a major part in regulating its ability to interact with microtubules	113, 119, 216, 223, 233
CK1, GSK-3, PKA, CAMKII	S409, S412, S413,	• Disrupts microtubule affinity-regulating kinase (MARK2)/PAR-1b and protein kinase A (PKA), both of which are involved in the regulation of microtubule stability and neurite outgrowth	119, 216, 222, 228, 229, 234
CAMKII, PKA, MARK	S416	• Serine 416 is strongly phosphorylated at early developmental stages in rat brain; therefore, CaM kinase II is involved in the accumulation of tau in neuronal soma in AD brain	222, 229, 235
MAPK, GSK3β, PKA, Cdk5, Dyrk1a, JNK, p38, TTKI	S422	• S422 on caspase cleavage of tau may partly explain the delayed appearance of Tau-C3-positive NFT; the eventual appearance of Tau-C3 reactive tangles makes it clear that phosphorylation takes place at S422 • Prevents segregation during the lower activity of caspase, but may be overwhelmed as caspase activity levels increase • Leads to defensive operation resulting in the suppression of tau protein cleavage. Lead to abbreviate the transition path in vivo leading to fibril formation or develop stability of filaments in AD	216, 228, 229, 236–239

Abbreviations: AD, Alzheimer disease; NFT, neurofibrillary tangles; JNK, c-JUN-NH_2-terminal kinase; PKA, protein kinase A; MAPK, mitogen-activated protein kinases; PHFs, paired helical filaments; PP, protein phosphatases.

maintained. In contrast, transforming growth factor beta receptor I (Tgfbr1) inhibitors downregulate the expression of Cdk5 and p35 kinase activity. Similarly, early growth response protein 1 (Egr-1) has a capacity to highly express in the presence of glucose by mediating TGF-β1-ERK1/2 pathway and its inhibition by siRNA downregulates p35 and Cdk5 scenario.[132] Moreover, protein–protein interactions regulate the activity of Cdk5 with the intervention of regulatory and target molecules having substantial association with nestin in approaching p35, demonstrating streamlined flow and continuation of Cdk5/p35 activity. The truncated form of p35 molecule, p25, acquires and gathers in higher amount in the brain of AD patients' neurons. This increases Cdk5 kinase activity by repelling the degradation of p35 to p25 and binding of p25 to Cdk5 reflecting its cellular location and alters its substrate specificity. Hyperphosphorylation of tau molecules by p25/Cdk5 complex reduces its ability to associate with microtubules, thereby inducing cytoskeletal disruption, morphological degeneration, and apoptosis. Therefore, various findings support the idea of indicating p35 cleavage and accumulation of p25 involvement in the pathogenesis of cytoskeletal abnormalities and neuronal death.[133] Cdk5 is also expressed in adipocytes to phosphorylate

proliferator-activated receptor gamma (PPARγ) which leads to metabolic syndromes such as T2DM.[134,135] High glucose levels induce the expression of p35 and Cdk5 through TGF–β1–ERK1/2–Egr-1 pathway leading to create high ROS.[132] ROS also induces tau hyperphosphorylation and neuroinflammation in AD and T2DM via increasing proinflammatory mediators and the expression of TNF-α, IL-1β, and IL-6, and apoptosis.[136,137]

CK1

CK1, a ubiquitous serine/threonine-selective protein kinase, is mainly expressed in the neurons. CK1 is involved in the tau hyperphosphorylation and Aβ production which has been evidenced by the increased levels of CK1ε protein or mRNA leading to elevated phosphorylation of many sites of tau protein such as S262, S356, and S214, involved in AD and T2DM.[121,138]

PKA and PKB

PKA and PKB, the two members of phosphoinositide-dependent PK, play a central role in cellular signaling by the process of phosphorylation. PKA phosphorylates many sites of tau such as Ser262 and Ser409 to increase cAMP levels as a prime for CK1 and GSK-3, whereas PKB phosphorylates this protein at Thr212 and Ser214 which promotes tau attachment to the 14-3-3 as studied in the in vitro model. Phosphorylation of tau at S241 by both PKA and PKB is associated with organization of microtubule cytoskeleton and formation of NFTs in AD.[139–141] These two kinases increase glucose uptake and inotropic effects in adipocytes and pancreatic cells, and glucotoxicity, as well as promote proliferation in the beta cells which are involved in progression of T2DM.[142] Blocking IP modulation of hepatic gluconeogenesis through PKA/CREB and PI3K-γ/PKC-ζ/TRB3/AKT pathway can also contribute to the T2DM progression.[143]

P38

P38 enzymatic activity in the MAPK reacts to the stress induction, in addition to apoptosis, leading to hyperglycemia that induces OS. This phenomenon, p38 MAPK pathway activation via tau protein phosphorylation, initiates development of AD and T2DM.[144,145] Many studies have shown that activated p38 is exclusively localized to the NFTs and coimmunoprecipitated with PHF-tau in the hippocampal and cortical brain regions of AD brain.[146,147]

MARK4

MARK4, also known as Par-1d/MarkL1, is a member of the AMPK, which is implicated in the regulation of glucose and energy homeostasis. Phosphorylation of the microtubule by this kinase causes its detachment from the microtubules. MARK selectively phosphorylates existing S262 and S356 emerged in every MBD and other proteins that influence microtubules to facilitate the formation of cell processes.[148,149] It was reported that MARK4 deficiency mitigated insulin resistance enhancing insulin-stimulated AKT phosphorylation in major metabolic tissues.[150]

PLK2

Upregulation of PLK2 (SNK) is mediated by the increased α-syn phosphorylation at S129 site which elevates pre-form of α-syn fibrils and with Aβ leading to tau hyperphosphorylation and reduction of tau binding to microtubules to promote the formation of NFTs-like aggregates in AD.[151,152] Tau phosphorylation leads to aggregation of this protein by co-expressing glycogen synthase and kinase 3 beta or MAP/microtubule affinity-regulating kinase 2 involved in the progression of T2DM.[153]

Syk

Syk, a tyrosine kinase of tau protein at tyrosine 18 and α-syn, probably could influence the function and physiology of neurons in the brain.[154] The tau in the detergent-resistant membranes is a tyrosine phosphorylated form which harbors lipid rafts. This form of tau protein is expected to facilitate a neurotoxic reactance towards Aβ. Syk can phosphorylate tau protein at Y18, Y197, and Y394 sites, respectively. Although other src family kinases may phosphorylate tau in the brain, PHF-tau is phosphorylated at tyrosine 394 and Fyn is the strongest candidate for tyrosine phosphorylation.[117,155,156]

DYRK1A

This kinase plays an important role in the signaling pathways which regulate cell proliferation and probably brain development. Dyrk1A mediates phosphorylation at the Thr356 and T181 residues of GSK3β that can inhibit its activity. Since DYRK1A pathway involves in the regulation of β cell mass and carbohydrate metabolism, defect in this protein could lead to T2DM.[157,158]

PPP

PPP group includes serine/threonine PP 1, 2A, 2B, and 5. Activity of PP2A in the normal brain is more than in AD brain (71% vs 50%), but activity of PP1 and PP5 in normal is less than in AD brain (11% and 10% vs 20% and 20%, respectively). PP1, PP2A, PP2B, and PP5 dephosphorylate tau protein at various sites, implicated in the stability and function regulation of microtubule. PP1 and PP2A are associated in a state where tau protein is hyperphosphorylated

significantly than the tau protein in normal brain. PP5 at a higher expression level affects phosphorylation spot by removing the phosphate groups. Thus, it promotes neurons preservation vs apoptosis induced by Aβ.[159,160]

P70S6K

Protein, p70S6K, accompanied with Ser-Thr kinase, phosphorylates the ribosomal S6 subunit, the fundamental sequel in cell cycle control, growth, and differentiation leading to tau accumulation by translation and upregulating the expression. At protein level, the epitope T421/S424 of p-p70S6K is associated with tau phosphorylation. These epitopes phosphorylate tau at S214, S262, and T212 sites in AD brain, and inhibit recombinant tau assembly in vitro. Activated p70S6K in NFT-bearing neurons might be caused by the aberrant regulation of P13K and MAPK pathways, as well as the reduced activity of PP2A in AD brain. Deposition of Aβ in the AD brain also contributes to activation of p70S6K and consequential formation of tau-associated pathologies in AD brain, P70s6k plays a critical role in the early development process of T2DM as well. IRs mediate PI3K and p70S6K activation during insulin stimulation.[161–163]

Aggregation and degradation of hyperphosphorylated Tau

Approximately 90% of APP can be processed by nonamyloidogenic pathway and the remaining is processed by amyloidogenic pathway.

Nonamyloidogenic pathway

In nonamyloidogenic or nonplaque-forming pathway, a transmembrane protein known as APP is segregated via α-secretase enzyme leading to the formation of carboxy terminus fragment α (CTFα) and soluble APP fragment α (sAPPα). Later, γ-secretase segregates CTFα, which ends up with the induction of APP intracellular cytoplasmic domain (AICD) and p3 peptide. Probably, the sAPPα, which is considered as neuroprotective factor, is associated with the establishment of synapses within the neurons, neurite outgrowth, and neuronal survival. AICD may be involved in nuclear signaling via transcriptional regulation as well as axonal transport through its ability to associate with various proteins.[164,165]

Amyloidogenic pathway

In the amyloidogenic or plaque-forming pathway, APP and β-secretase are interposed within the endosome with an acidic environment, inducing β-secretase to segregate APP protein, following the formation of CTFβ and soluble APP fragment β (sAPPβ). Consequently, CTFβ is cleaved by γ-secretase enzyme to form AICD and Aβ fragments. Later, sAPPβ together with Aβ liberates into the extracellular environment where Aβ fragments accumulate to form plaques.

Aβ aggregation and plaque formation

Aβ peptide chain contains 38 ($Aβ_{38}$), 40 ($Aβ_{40}$), or 42 ($Aβ_{42}$) amino acids. $Aβ_{42}$ is chemically stickier compared with the other peptides. All three genetic mutations that cause early-onset AD change the role of gamma secretase, leading to an increased production of $Aβ_{42}$.[166,167] Aβ peptides aggregate into oligomers to organize fibrils with the formation of AP. Aβ plaques block signaling pathways and cells connection, which can be lethal to cells. Further, it can cause NTFs formation and Aβ is thought to cause oxidative damage to the cells. Along with the development of NFTs, low levels of insulin can increase the Aβ levels and forms AP in the brain. The Aβ peptide acts as monomers, dimers, or multimers on cell membranes and binds to its receptors on neuronal and glial cells at the nanomolar concentration to interfere with neurotransmission and memory before the AP builds up.[5,168,169]

Insulin–amyloid plaque–neurofibrillary tangles

Insulin regulates peripheral Aβ and tau metabolism which influences the Aβ release in the brain through regulating APP metabolism to modulate the balance between Aβ anabolism and catabolism.[170] Lack of insulin or its action may link T2DM to AD by modification of Aβ production and degradation. Defect in the insulin-dependent pathways may increase the activation of GSK3 associated with the risk of AD. T2DM also modifies mitochondrial antioxidant defense system and assists brain weakness in the presence of Aβ toxicity.

A link between the involvement of insulin-degrading enzyme (IDE) in hyperinsulinemia and AD is closely related to dysfunction in the metabolic and neurological pathways.[171,172] IDE is a thiol zinc-metallo-endopeptidase that cleaves small proteins such as insulin, Aβ, glucagon, calcitonin, and amylin which leads to the formation of β-pleated sheet-rich amyloid fibrils under certain conditions; levels of insulin together with Aβ in the brain are regulated by IDE. Interestingly, the hypofunction of this enzyme triggers the formation of AD and T2DM.

Role of antidiabetic drugs on Alzheimer's disease

The incidence of MCI more often seen in T2DM patients may develop to AD. Therefore, improvement in cognition with antidiabetic drugs could be a strategy rather than mere glycemic control. Interestingly, these drugs could benefit

AD patients associated with T2DM and it remains to be determined whether the potential is due to glucose lowering or the neuroprotective effects. However, further research is warranted to investigate their links between cognitive impairment and AD, and their safety measure is important too when considered in the management setting.

We highlight the potential of antidiabetic drugs with experimental and clinical observation through numerous studies that would be of interest to the researchers in developing strategies and linking in-depth mechanisms.

Biguanides

Metformin is an oral hypoglycemic drug under biguanide class used in the treatment of diabetes. In experimental studies, metformin showed neuroprotective role by preventing etoposide-induced apoptotic cell death in primary neurons and improved oxygen-glucose in neuronal injury. McNeilly, in 2013, demonstrated that in high fat-diet-induced animals, metformin attenuated the insulin resistance and weight gain, but had no effect on performance in either massive transfusion protocol (MTP) or no MTP (nMTP) tasks. In addition, metformin has shown to prevent the appearance of molecular and pathological characteristics of AD in neuroblastoma cell line model of insulin resistance. Interestingly, in diabetic rat model, metformin has revealed the reduction of cell proliferation and neuroblast differentiation in hippocampal dentate gyrus.[173–176]

Ng et al investigated the effect of metformin on the risk of cognitive impairment and its possible modulation by apolipoprotein E (ApoE) ε4 gene polymorphism. Metformin did not show any significant interactive role with ApoE ε4 and depression. Interestingly, among individuals with diabetes, long-term treatment (>6 years) reduced the risk of cognitive decline.

On other hand, the clinical studies on metformin show that the subjects aged 50 years and older significantly decreased the risk of dementia when compared with non-medication group after adjustment for cerebrovascular disease.[177] In contrast, a case–control study displayed that long-term users of metformin were at greater risk of developing AD.[178] Similarly, a study which included AD and cognitively intact patients showed worse cognitive performance in metformin users compared with those who were taking metformin and calcium together.[179] Altogether, these studies raise the possible confounding effects of metformin in the management process of AD/neurological function, and therefore needs further understanding through molecular biomarkers approaches in clinical studies.

Sulfonylurea

Sulfonylureas such as glyburide and glipizide inhibit mTOR activation in the experimental model, as we know aberrant PI3K/mTOR activation is commonly experienced in diabetes and AD.[180] Glyburide has been shown to inhibit inflammasomes responsible for the elevation of proinflammatory cytokines resulting in neuroinflammation associated with AD.[181]

In clinical studies, sulfonylureas do not alter the risk of developing AD in a long-term population-based case–control study.[178] However, combination of metformin and sulfonylureas in a prospective cohort study over the period of 8 years reduced the risk of dementia by 35%, but their efficacy in preventing or improving memory and cognition needs to be determined.[177]

Thiazolidinediones

Thiazolidinediones such as rosiglitazone and pioglitazone might have role in reducing the risk of neurodegeneration.[182] Rosiglitazone has shown protective effects in experimental models against neuronal insulin resistance induced by beta amyloid oligomers.[183] On the other hand, pioglitazone showed improved cognitive performance in a rat model of memory impairment.[184]

In randomized controlled trial (RCT), rosiglitazone preserved memory function in patients with early AD and amnestic MCI but beta amyloid continued to be stable in plasma.[172] Another small randomized double-blind trial on rosiglitazone demonstrated improvement in cognitive function in mild-to-moderate AD patients who were not carriers of the ApoE ε4 allele.[185] In multicenter randomized concept clinical trial, rosiglitazone ameliorated impairment of brain glucose metabolism in mild-to-moderate AD subjects, but did not show evidence of slowing clinical progression.[186] Another RCT on pioglitazone significantly decreased AD assessment scale (ADAS) score in AD/MCI subjects.[187] In contrast, Phase III trial on rosiglitazone monotherapy failed to show a benefit on cognitive outcomes in mild-to-moderate AD.[188] Similarly, another population–based case–control study did not change the risk of developing AD.[178]

Glucagon-like peptide 1

Another study on GLP-1 receptor agonists, liraglutide and lixisenatide, reduced the hippocampal burden and improved spatial memory in AD transgenic mice.[189] Liraglutide ameliorated tau hyperphosphorylation and restored brain insulin sensitivity in type 2 diabetic rats.[190] Thus, liraglutide diminishes neurodegenerative developments in AD.

Overall, preclinical and clinical studies support the efficacy of antidiabetic drugs in cognitive enhancement; some studies have failed to confirm reports of improved cognition in patients with T2DM even after good glycemic control. However, more clinical studies on antidiabetic drugs in agreement with preclinical approaches would enhance the chance of correlating MCI/AD for better therapeutic strategy and thereby increase the quality of life in AD patients.

Conclusion

This review extracted valuable outcomes from the studies that described the underlying common mechanisms between T2DM and AD, and the molecular determinants which could have significant therapeutic potential in treatment of T2DM- and/or AD-related damages. It was concluded that those patients who develop T2DM often suffer from dementia which might be AD. These patients could also suffer from hyperglycemia, hypercholesterolemia, and insulin signaling dysfunctions which are common features to T2DM. In addition, some antidiabetic drugs could have beneficial effects against some AD hallmarks, such as tau hyperphosphorylation, Aβ plaque formation, and apolipoprotein particularly ApoE4. Therefore, cardiometabolic signaling needs appropriate crosstalk to understand the mechanism and linkage with neuroinflammation process in the neurodegenerative disorders.

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Author contributions

SKR was involved in the writing and original draft preparation, AA was involved in the supervision, writing, and editing of the manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

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